OBSERVATIONS

Prevalence of Eating Disorders in Young Patients With Type 1 Diabetes From Two Different Italian Cities

The prevalence of eating disorders and behaviors was evaluated in two populations of adolescents with type 1 diabetes from two cities in Italy. In this report, we will establish the relationship of these disorders with sex, BMI, socioeconomic status, metabolic control, and compliance to therapy.

A total of 193 patients with type 1 diabetes aged 8–18 years (mean 13.6 ± 2.7 years; 92 female and 101 male subjects) were recruited from the pediatric diabetology units at the Second University of Naples ($n = 118$, 56 female and 62 male subjects) and at the University of Parma ($n = 75$, 36 female and 39 male subjects).

All patients were affected by type 1 diabetes without evidence or history of other autoimmune diseases (thyroiditis, celiac disease, etc.). The distribution of sex, age at the onset of diabetes, disease duration, and BMI was statistically similar in the two groups. A total of 63.1% of the patients (64.6% from Naples and 35.4% from Parma) were from families with low socioeconomic status (according to the annual income and the parents' level of schooling). The mean BMI was 21.45 ± 3.45 kg/m². Almost all patients were on intensive insulin therapy (43% on three administrations/day 54.8% on four administrations/day). All patients completed the Eating Disorder Examination Questionnaire (EDE-Q) (2,3), which was modified for diabetes (2,3) and the diabetes compliance scale (4). A total of 131 healthy control subjects from Naples and Parma, matched for age and sex, completed the EDE-Q.

No major eating disorders, such as anorexia and bulimia nervosa, were found in patients with diabetes or in healthy control subjects. Otherwise unspecified minor eating disorders that do not meet the DSM-IV criteria for anorexia and bulimia nervosa, such as binge eating, overeating (with and without loss of control), and inappropriate compensatory behavior were more frequent in patients with diabetes than in control subjects (9 of 181 patients who answered this specific item vs. 1 of 131 control subjects, $\chi^2 = 2.883$, $P = 0.09$).

Binge eating episodes were reported by 49.7% of diabetic patients and by only 24% of control subjects ($P = 0.002$). The presence of this disturbance was found more frequently in patients with low social status ($P = 0.003$). Objective overeating was present in 41.9% of patients and only in 16.9% of control subjects ($P = 0.0001$), while the difference between the report of subjective overeating was not significant between patients and control subjects.

The prevalence of inappropriate compensatory behaviors such as voluntary vomiting, self-administration of diuretics and laxatives, and excess physical exercise have been found to be slightly more frequent in diabetic patients (9 of 181 patients who answered this specific item vs. 1 of 131 control subjects' answers, χ^2 $P = 0.074$). If we consider the skipping or manipulating of insulin dosage to lose weight as a sign of body dissatisfaction and therefore as an otherwise unspecified eating disorder, the total prevalence of eating disturbances in diabetic patients is significantly higher (χ^2 $P = 0.002$) than in control subjects. We recognize that this may not be an entirely valid comparison because control subjects do not have the opportunity to manifest episodes of otherwise unspecified eating disorders by manipulating insulin doses. On the other hand, insulin omission and/or dose manipulation offers a unique resource to patients with diabetes to manifest his/her concern about body image. All together, the behaviors in our study were reported by 25 of 192 patients and 1 of 131 control subjects ($\chi^2 = 12.273$, $P = 0.0001$).

The presence of eating disturbances was only slightly correlated to the reported compliance. In people with the highest mean score on the diabetes compliance scale (mean = 8), the prevalence of eating disturbances was 11%. When the mean score was lowest (mean = 4), it increased to 17% ($\chi^2 = 5.331$, $P = 0.021$).

In conclusion, in our study, anorexia and bulimia nervosa are not common in adolescents and young adults with type 1 diabetes, while otherwise unspecified eating disorders seem to be more common than in healthy control subjects. There was no difference in eating disorder prevalence between control subjects and patients from two different cities and eating habits, but the prevalence appears correlated only to socioeconomic status and low compliance to therapy.

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Hypoglycemic Coma in a Diabetic Patient on Peritoneal Dialysis due to Interference of Icodextrin Metabolites With Capillary Blood Glucose Measurements

Continuous ambulatory peritoneal dialysis is used in about one-third of the diabetic population as an alternative to hemodialysis for end-stage renal disease (ESRD). Several case reports and articles (1–3) have alerted health professionals on the potential interference of dialysis fluid containing 7.5% icodextrin, a cornstarch-derived glucose polymer (Extraneal; Baxter Healthcare, Castlebar, Ireland), with some glucose reagent systems using a glucose dehydrogenase enzyme with coenzyme pyrroloquinolinequinone (GDH-PQQ). Overestimation of capillary blood glucose readings have led to critical situations where severe hypoglycemia was not detected. This source of errors has recently led to specific recommendations, including those from the manufacturers of glucose test strips. Despite this, we observed one recent case of severe hypoglycemia in our institution due to treatment of a false hyperglycemia by high doses of fast-acting insulin. A 50-year-old woman with a 33-year duration of type 1 diabetes was hospitalized in the Department of Nephrology for a pretransplantation evaluation 6 months after the beginning of peritoneal dialysis. A capillary blood glucose value of 410 mg/dl at 4:00 P.M. was found using a hospital monitoring system (AccuChek active; Roche Diagnostics, Mannheim, Germany). After an additional 12 units of fast-acting insulin, the patient developed a hypoglycemic coma 1 h later and recovered rapidly after an intravenous injection of glucose. This episode may reflect that many professionals are still unaware of this potentially life-threatening effect. Beside icodextrin interference, low hematocrit and high uric acid (4) may also lead to false blood glucose results in patients with ESRD (2). In most institutions, glucose monitoring systems are delivered to clinical units based on reduced risk for viral cross-contaminations and economical factors. Therefore, for patients on continuous ambulatory peritoneal dialysis, it is highly recommended to test the validity of any glucose analyzer by cross-checking the results with the laboratory reference method and exclude the use of all GDH-PQQ–based meters for patients with ESRD and for hospitals taking charge of complicated diabetic patients.

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Resolution of Diabetic Cheiroarthropathy After Pancreatic Transplantation

A 51-year-old man was referred to our unit with a 12-month history of progressive impairment of hand function. He was unable to make a fist and had difficulty picking up small objects. He did not describe any joint pain, swelling, or morning stiffness, and there were no features to suggest an inflammatory arthropathy. He had been diagnosed with type 1 diabetes at age 7 years, complicated by diabetic nephropathy requiring a renal transplant 20 years previously (for which he was on long-term ciclosporin) and retinopathy.

On examination, his skin appeared slightly thickened. He had contractures evidenced by a positive prayer sign and was unable to flatten his hands completely. The remainder of the physical examination was unremarkable except for a functioning renal transplant; specifically, he had no evidence of synovitis or neuropathy. Laboratory investigations, including erythrocyte sedimentation rate, C-reactive protein, and rheumatoid factor, were normal. His HbA_{1c} was 6.0%. Hand radiographs were unremarkable. He was treated with physiotherapy and wax for a presumed diagnosis of diabetic cheiroarthropathy with little improvement in his symptoms. He had a successful pancreatic transplant 2 months later, and his immunosuppression was changed to mycophenolate mofetil, tacrolimus, and a reducing course of prednisolone. His symptoms began to improve within a few weeks of surgery, and 6 weeks later he had full range of movement in both hands. His HbA_{1c} was reduced to 5.2%. One year later, he remains asymptomatic with normal hand function.

Diabetic cheiroarthropathy is characterized by skin thickening and restriction defined as "the inability to extend the metacarpophalangeal joints fully" (1) and is thought to be caused by collagen abnormalities and increased glycation of connective tissue. Studies suggest that cheiroarthropathy is associated with type 1 diabetes (2), duration of diabetes (3,4), and secondary complications (2,4). Treatment is often unsatisfactory, involving corticosteroid injection or surgery in severe cases. It is suggested that improved glycemic control may improve symptoms, although it is not usually associated with complete resolution.

Pancreatic transplantation is currently the only therapy for type 1 diabetes that re-establishes endogenous insulin secretion, rendering the recipient euglycemic. Follow-up studies of pancreatic transplant patients suggest that complications, including retinopathy, nephropathy, and neuropathy, are stabilized. Several studies report reversal of nephropathy (5,6), although it is suggested

this can only be expected after a long observation period (6).

This is the first case we are aware of in which cheiroarthropathy has been noted to resolve posttransplantation and highlights two potential mechanisms of cheiroarthropathy. Firstly, the early improvement on corticosteroids suggests an inflammatory component, which other authors have postulated (7), although the sustained improvement suggests that this is not simply a steroid effect but may reflect other factors such as a change in immunosuppression. Secondly, an alternative hypothesis suggests that the improvement in glycemic control may lead to resolution of symptoms, although the speed of improvement makes this less likely.

In conclusion, we observed the resolution of diabetic cheiroarthropathy after successful pancreatic transplant, which raises interesting potential mechanisms of cheiroarthropathy.

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The Korle-Bu Hb Variant in Caucasian Women With Type 1 Diabetes

A pitfall in the assessment of diabetes control

Measuring HbA_{1c} concentrations in diabetic patients is an established procedure for evaluating the long-term control of diabetes. The Diabetes Control and Complications Trial confirmed the direct relationship between diabetes complications and HbA_{1c} levels in type 1 diabetic patients. As a result, both the American Diabetes Association and the European Group for the Study of Diabetes have drawn up guidelines for assessing glycemic control by measuring HbA_{1c} levels. However, in spite of advances in standardizing methods for measuring HbA_{1c} concentrations, an increasing number of Hb variants produce false HbA_{1c} determinations.

We report the first case of the Korle-Bu Hb variant in a Caucasian woman, which is also the first case described in a diabetic subject. We also describe the interference of this variant in some of the methods used to determine HbA_{1c} concentrations. In our patient, HbA_{1c} levels were underestimated for 20 years and, as a result of this misleadingly good metabolic control, the patient has developed microangiopathic diabetes complications.

A 29-year-old Caucasian type 1 diabetic woman was referred to our center in order to optimize her glycemic control because she was planning to become pregnant. Diabetes had been diagnosed 20 years earlier, and she had since been treated with NPH insulin twice a day. Glycemic control had been relatively acceptable (laboratory HbA_{1c} ∼7–7.5%; reference values 4–6%) from the start. Her therapeutic treatment was changed to multiple insulin injections (regular insulin before breakfast, lunch, and dinner and NPH insulin at bedtime), and screening for diabetes complications was started. Severe retinopathy requiring laser therapy was found, and symptomatic peripheral neuropathy was confirmed after an electromyographic study. Fortunately, the urinary albumin excretion rate was normal, and no macrovascular complica-
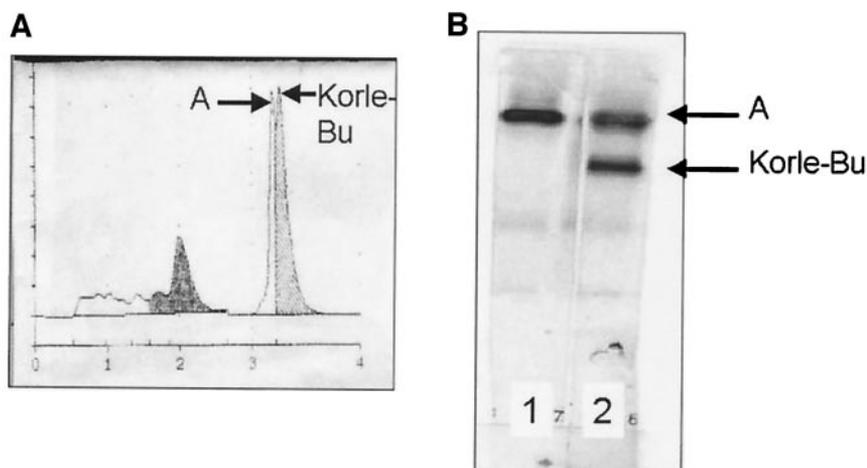

Figure 1—*Hb separation of the patient by automated HPLC and cellulose acetate electrophoresis. The Hb Korle-Bu was partially eluted with HbA_2 on HPLC (A) but was separated on electrophoresis (B). The migrations of HbA and Korle-Bu are identified by arrows. Lane 1, father; lane 2, patient.*

tions were found. After 2 months of the new therapeutic approach, HbA_{1c} levels were measured by her reference laboratory and a value of 3.9% was obtained. However, capillary glucose measurements did not agree with that result due to the absence of frequent hypoglycemias. We decided to measure HbA_{1c} again at our center using the DCA 2000 system (reference values <6%) and obtained a value of 6.9%. Three months later, HbA_{1c} levels were measured by her reference laboratory and also at our center using the DCA 2000 system. The discrepancy was confirmed again (3.7 vs. 6.7%, respectively), demonstrating that the laboratory had underestimated the HbA_{1c} value by ~50%. It was suspected that a Hb variant might be present that could not be properly detected by the laboratory's system, so electrophoretic analysis of the Hb was performed. An abnormal band was detected and, after sequenciation, corresponded to a Korle-Bu Hb variant present in heterozygosis of 40% (Fig. 1). A study of the family showed the same mutation to be present in her mother. Her brother chose not to be tested, and no other relatives were available for study.

More than 700 characterized Hb variants have been reported (1). The Korle-Bu variant of Hb, also known as Hb G-Accra, is one of the variants affecting the molecule's β-chains. It is the consequence of a mutation in codon 73 of the Hb gene (GAT→AAT), causing a single amino acid substitution in the β-chain (Asp→Asn). This mutation is very uncommon and has only been described in a few cases affecting black families from Ghana, Ivory Coast, Jamaica, Mexico, and Costa Rica (2–5). To our knowledge, this is the first reported case to date in a Caucasian subject. The patient said her family was from Spain and denied having any ancestors from other countries or of a different ethnic origin. In heterozygosis, no phenotypic abnormalities have been detected in the subjects carrying the mutation. Hematology is normal, and no modifications in oxygen affinity or Hb stability have been found. No homozygote cases have been reported.

All of the few cases of subjects with the Korle-Bu Hb variant reported to date corresponded to subjects screened to determine the prevalence of Hb variants in different populations. No cases involving diabetic subjects had been described be-

fore, and the effect of the variant on HbA_{1c} determinations was unknown.

There are different methods for measuring HbA_{1c} concentrations (6–8). The most frequent are boronate affinity or affinity-binding chromatography, cation-exchange chromatography, and automated high-performance liquid chromatography (HPLC) methods and immunoassays. Other methods include electrospray mass spectrometry and electrophoresis. Our patient's HbA_{1c} levels were measured at a laboratory using a well-validated HPLC method (Menarini HI-AutoA$_{1c}$ HA-8121). This method separates Hb species based on charge differences. Hb species elute from the cation-exchange column at different times with the application of buffers of increasing ionic strength. A spectrophotometer measures the concentration of Hb in each collected fraction, which is quantified by calculating the area under each peak. The following equation makes it possible to determine the amount of HbA_{1c} in a given sample: percentage HbA_{1c} = 100 × ([HbA_{1c}/HbA] + HbA_{1c}). In our case, the Hb variant (called HbX_{1c}) and HbA_{1c} separate, whereas HbA and HbX coelute, producing a spurious decrease in the calculated value of the percentage of HbA_{1c}. The system used at our center to measure HbA_{1c} (immunoassay method; Bayer DCA 2000) is based on antibodies that recognize the NH_2-terminal–glycated amino acid in the context of three amino acids of the Hb β-chain. These antibodies do not recognize other glycated Hb species, including chemically modified derivatives. The system is not affected by the Korle-Bu variant, which does not fall within the susceptible region.

We can conclude that glycemic control in diabetes must be evaluated not only through periodical HbA_{1c} determinations but also with the information obtained from capillary glucose measurements. Any discrepancy found between the HbA_{1c} and fingerstick measurements should be analyzed carefully, and the possible presence of Hb variants should be taken into account.

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COMMENTS AND RESPONSES

Short-Term Intensive Insulin Therapy in Newly Diagnosed Type 2 Diabetes

Response to Ryan, Imes, and Wallace

The recent report by Ryan et al. (1) demonstrated that in newly diagnosed type 2 diabetes, a short course of intensive insulin therapy successfully laid a foundation for long-term good gly-

cemic control and suggested that the only predictors that could be maintained on diet alone in the long term were those concerned with the ease with which glycemic control could be achieved. We agree with their strategy of short-term intensive insulin therapy to restore β-cell insulin secretion and/or insulin action that is impaired by glucose toxicity in cases of severe newly diagnosed type 2 diabetes.

Glucose toxicity has two different aspects: impaired insulin secretion (2) and decreased insulin action (3). In their report, however, the authors did not precisely discuss which mechanism (insulin secretion or action) was predominantly recovered or not rescued in better responders (diet-alone group) and lesser responders (oral hypoglycemic agent [OHA]/insulin group) with intensive insulin therapy in a short period. According to their results, both the area under the curve (AUC_i) (their Fig. 1*B*) and the insulin-to-glucose ratios at the 30-min point in a post–insulin therapy oral glucose tolerance test (OGTT) were not different between the diet-success and diet-failure groups, suggesting that restoration of insulin secretion was similar in both groups. Although the authors selected newly diagnosed type 2 diabetic subjects with similar hyperglycemia, it is important to assess whether the disease duration after onset of diabetes was the same in both groups, because duration of diabetes may be a key predictor of the reserve of insulin secretion.

With regard to insulin resistance, the authors did not provide the clinical parameters of insulin resistance such as homeostasis model assessment of insulin resistance (HOMA-IR). They showed that with the post–insulin therapy OGTT, the fasting insulin-to-glucose ratio was higher in the diet-failure group, despite a higher fasting glucose level (fasting insulin level was not shown), than in the diet-success group, meaning greater insulin resistance in the diet-failure group. The BMI values of each group before insulin therapy were similar, but it is possible that a type II error was present because of very small sample numbers. Moreover, the BMI in the diet-only group was significantly reduced at 6 months, while that in the OHA/insulin group did not change throughout the study. Taken together with their results, we consider that insulin sensitivity or resistance rather than insulin secretion may deeply influence the

need for OHAs or insulin after short-term intensive insulin therapy in their study. Additional larger prospective studies are needed to use intensive insulin therapy in clinical practice in newly diagnosed type 2 diabetes.

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Short-Term Intensive Insulin Therapy in Newly Diagnosed Type 2 Diabetes

Response to Yoshioka, Yoshida, and Yoshikawa

We thank Yoshioka, Yoshida, and Yoshikawa (1) for their interest and comments on our article (2) on the use of a short course of intensive insulin therapy in newly diagnosed type 2 diabetic patients. We are pleased that they think this strategy has merit. Our study was an initial pilot study and did not in-

clude detailed measures of insulin sensitivity, and we acknowledge this in the article.

Yoshioka, Yoshida, and Yoshikawa make the point that insulin secretion increased equally in both the diet-responsive group and those needing oral hypoglycemic agents (OHAs) or insulin. There was a higher basal insulin-to-glucose ratio in the diet-failure group at the end of the short course of insulin therapy, suggesting more insulin resistance. They consider that insulin resistance, rather than insulin secretory defects, influences the need for OHAs or insulin after a short course of insulin treatment in newly diagnosed type 2 diabetic subjects.

We agree that less insulin resistance was a better predictor of longer-term success on diet alone and made this point in our discussion of the results when we state that those who normalized their glucose more readily with less insulin are, by definition, more insulin sensitive and "this may be an underlying contributor to their longer-term success." We also point out that the difference in the insulin-to-glucose ratio after the course of insulin therapy did not reach statistical significance. The homeostatis model assessment of insulin sensitivity (3) after the course of insulin therapy was significantly higher in the diet-only group ($86.4 \pm 12.2\%$) than in the OHA/insulin group ($50.2 \pm 6.3\%$, $P = 0.014$). It should be recalled that in posttherapy, the exogenous insulin was held the night before the test but the recently prior exogenous insulin may interfere with the model assessment. Irrespective of these tests, we feel that the better response to insulin in the diet-only group demonstrates a priori increased insulin sensitivity. As we noted in the discussion, an unknown is the duration of the diabetes prediagnosis, which may be important.

We agree that insulin sensitivity is an important determinant of the longer-term success demonstrated. However, given the further increase in insulin area under the curve at 1 year in both groups, it is clear that insulin secretion had not reached its maximum potential and thus the insulin secretory defect is important. We concur that the area is deserving of further study.

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Deficiency in the Detection of Microalbuminuria by Urinary Dipstick in Diabetic Patients

Response to Comper et al.

We read with interest the letter from Comper et al. (1) that compared the performance of Bayer's Microalbustix and CLINITEK Microalbumin urinalysis strips with a high-performance liquid chromatography (HPLC) method that allegedly detects nonimmunoreactive forms of albumin. The Comper et al. letter implies that the American Diabetes Association established the >95% detection criteria for semiquantitative microalbuminuria tests on the basis of this HPLC reference method.

This implication is misleading. The American Diabetes Association criteria were not likely based on the Comper et al. method of detecting nonimmunoreactive forms of albumin because that method is neither standardized nor commonly used. Furthermore, the suggestion of Comper et al. that Bayer product performance is deficient in this area is not supported by available evidence.

Standard immunoassay and chemical methods for measuring albumin do not detect nonimmunoreactive forms of albu-min. Moreover, we are not aware of any National Bureau of Standards traceable standard containing the nonimmunoreactive form(s) of albumin, albumin fragments, and/or albumin aggregates combined with standard immunoreactive albumin in the correct proportions to standardize the HPLC method referenced in the Comper et al. letter.

To our knowledge, there is no peer-reviewed publication proving that nonimmunoreactive forms of albumin provide earlier kidney disease detection in humans compared with standard albumin. Comper et al. provided no performance data to show the false-positive rate for kidney disease detection when nonimmunoreactive forms of albumin, albumin fragments, and/or albumin aggregates are measured. To determine the clinical false-positive rate, a diagnostic work-up on all patients in the study would need to be done. This could include one or more of the following: glomerular filtration rate, creatinine clearance, urine sediment analysis, ultrasound, imaging, or persistent microalbuminuria (standard form of albumin). If no evidence of disease is found from established methods, it is unclear whether a patient with nonimmunoreactive albumin in their urine has early kidney disease.

Bayer is committed to the early detection of kidney disease and has a keen interest in new markers that are proven to advance the diagnosis of kidney disease. Bayer CLINITEK Microalbumin product sensitivity has been demonstrated at 97–98.4% when compared with standard albumin and creatinine assay methods that are accepted by health professionals managing patients with diabetes (2,3).

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Deficiency in the Detection of Microalbuminuria by Urinary Dipstick in Diabetic Patients

Response to Selgren

We would like to assure Selgren (1) that in 2002, the American Diabetes Association could find no published study that fulfilled their requirements of a detection rate of >95% for abnormal samples from patients with microalbuminuria for qualitative (or semiquantitiative) dipstick tests. This was quite independent of measuring albumin by the high-performance liquid chromatography (HPLC) method. We only noted that the American Diabetes Association came to the same conclusion as we did using the HPLC method.

In relation to performance data, the HPLC method has been cleared by the Food and Drug Administration (FDA) (August 2003) as a test to measure albumin. FDA labeling states that "the HPLC method permits a direct measurement of intact albumin, regardless of the reactivity potential of the protein with antibodies. Since immunoassays (and dye binding assays) may not detect all of the intact albumin in urine samples it is expected that the HPLC technology will, depending on the specimen, report greater urinary albumin values when compared to immuno-chemical urinary albumin test systems and dipstick systems."

There has been a recent publication in *Kidney International* (2) demonstrating that the HPLC technique provides earlier detection of kidney disease in humans than the standard albumin assay. The mean lead time for the HPLC assay to detect microalbuminuria versus a radioimmunoassay was 3.9 years for type 1 diabetic patients, with a 95% CI of 2.1–5.6 years. For type 2 diabetic patients, the

mean lead time was 2.4 years, with a 95% CI of 1.2–3.5 years.

We emphasize that the HPLC assay measures intact albumin directly, but it will not measure albumin aggregates or albumin-derived fragments. In relation to the Bayer dipstick (microalbustix and CLINITEK microalbumin), we have not seen any published information as to what the dipstick detects (i.e., albumin aggregates, glycated albumin, albumin with lipid or other ligands, or denatured albumin or albumin fragments). All these forms of albumin may exist in urine. All we know is that the Bayer dipsticks give high false-negative rates when compared with an FDA-cleared test that quantitatively detects intact albumin.

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A Systematic Review of Adherence With Medications for Diabetes

Response to Cramer

The recent article by Cramer (1) aroused our full interest. The author reports a systematic literature search performed to identify articles with quantitative data on adherence to oral hypoglycemic agents and insulin and correlations between adherence rates and glycemic control. Abstracts identified by searching Medline, Current Contents, Health & Psychological Instruments, and Cochrane Collaborative databases were screened. The systematic search resulted in 20 publications, i.e., 15 retrospective and 5 prospective studies, with adequate data for synthesis. We would like to suggest that from our experience, the Embase database would have probably added relevant, high-quality articles that do not appear in these databases.

In searching the literature on interventions for improving adherence to treatment recommendations in people with type 2 diabetes (2), we evaluated the input from different databases. Exhaustive searches were performed with peer-reviewed search strategies in the following databases: the Cochrane Library (including the Cochrane Controlled Trials Register, the Database of Reviews of Effectiveness, and the National Health Service Health Economic database), the Metabolic and Endocrine Disorders Group specialized register, Medline, Embase, Psychinfo, Eric, Dissertation and Sociological Abstracts, Cinahl, and the metaregister of controlled trials. Studies were included when interventions aimed at improving the adherence to treatment recommendations in people affected by type 2 diabetes.

Overall, we retrieved 3,210 publications, mainly originating from three core databases: Medline, Embase, and the Cochrane Collaboration databases. Two teams of independent researchers read all abstracts. When insufficient information was available to evaluate the study, the full article was retrieved. A total of 35 prospective studies were included.

We were eager to know which databases were able to identify the majority of the included articles and what the overlap could be between different databases. Of 1,684 Medline hits, 12 articles (0.71%) were included for data extraction. Embase resulted in 21 articles out of 1,165 hits (1.80%), and the Cochrane Library resulted in 17 articles out of 341 hits (4.99%). Five articles were cited by all three databases; 21 of 33 articles were cited only once. Of these, 10 were located by Embase, 8 by Cochrane, and only 3 by Medline. If we had only identified articles from Medline, our search would have identified 12 of 33 articles (36.4%). If we had searched only Embase, the outcome would have been 21 (63.6%), and, if we had searched only the Cochrane database, the result would have been 17 (51.5%).

Our key message is that searching in all relevant databases is a must for what is called a systematic literature search. Electronic databases enhance the accessibility of evidence. This supports researchers in being comprehensive. Free access to all databases for research purposes could even improve the outcome.

Being systematic means being exhaustive, which means being as complete as possible, resulting in a harvest of all available research evidence on the topic of interest (3). A partial approach, being systematic without searching all databases, could be synonymous to bias. Is not bias exactly what a researcher would want to avoid in being systematic?

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A Systematic Review of Adherence With Medications for Diabetes

Response to Wens et al.

Wens et al. (1) comment on the value of using multiple databases to search the literature for my report (2). However, they do not mention another technique that I have found to be valuable: checking the reference lists of articles found in database searches and other sources. This manual method overcomes reliance on electronic searches by key word. Relevant reports are often missed in electronic searches because they are focused on another end point (e.g., efficacy, adverse events, etc.), so the list of key words does not include terms for medication compliance/adherence or persistence. Careful reading of the article will lead to a relevant article containing pertinent data.

The results of the multimodal search noted by Wen et al. was not for adherence/compliance or persistence data but for another topic. They do not actually demonstrate flaws in the search that I used for my report on adherence with medications for diabetes. Had they performed the same search, they might have found fewer differences because my search required that articles include specific data on adherence/compliance rates or persistency duration. Of course, the time lag between performing a search and publication of the report is lengthy. I also found additional articles that were published during this period that have yet to be reported. The results of my previous literature searches on adherence/compliance rates have been consistent over time, with little difference in my overall finding that patients take approximately three-fourths of medication as prescribed (3), particularly when electronic dose monitoring is used as the method (4).

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The GILHT-E Syndrome?

The announcement of the new section in *Diabetes Care* (Metabolic Syndrome/Insulin Resistance Syndrome/Pre-Diabetes) by Davidson (1) and the response by Vinicor and Bowman (2) point out that there is no consensus on the name, components, or treatment of the constellation of risk factors that is associated with cardiovascular disease. I would like to suggest that the constellation may be important primarily as an etiological concept—that the constellation implies the existence of a common underlying factor linking its components. Further, the presence of a common underlying factor, which could lead directly to myocardial infarction (MI), increases the possibility that any one or more of the components of the constellation could be incidental to the development of MI (3). An underlying factor, if identified, could define the components of the constellation and provide a focus for their treatment as well as for the prevention of MI. I suggest that the underlying factor may not be insulin resistance, as proposed by Reaven (4) and generally accepted as the prime suspect, but rather an increase in visceral adipose tissue (VAT) that may be secondary to an alteration in the sex hormone milieu.

In 1977, I reported correlations of glucose, insulin, cholesterol, and triglyceride with each other and with sex hormones in men with MI and control subjects (5). I hypothesized that the risk factors for MI were part of a "glucose-insulin-lipid defect" that was secondary to an increase in the estradiol-to-testoster-

one ratio (E/T). I also noted an association of this defect with hypertension.

The following year, I reported that glucose intolerance, hyperinsulinemia, hyperlipidemia, and hypertension concurred to form a constellation of factors that occurred not only with MI, but also with obesity, aging, and other clinical states (6). The observation that these risk factors concurred in other clinical states, as well as MI, provided further evidence that the risk factors were related to each other and linked by a common underlying factor. That the other clinical states were also associated with alterations in the levels of sex hormones supported the hypothesis that an increase in E/T or a closely related alteration might be the underlying factor for the constellation (6). I also suggested that obesity could induce the constellation and be both a cause and a result of the hormonal alteration (6). All of the major and most of the more recently identified risk factors for MI have since been reported to be associated with sex hormone levels (7–9). Moreover, a low testosterone level has been reported to be prospective for the "metabolic syndrome," as well as for diabetes, in men (10).

In a recent study in men in which we had measurements of body composition, we compared the relationships of sex hormones, insulin, and adiposity variables with each other and with risk factors for MI and found that correlations of sex hormones and insulin with risk factors lost significance after controlling for VAT. We concluded that an increase in VAT is the most likely factor directly underlying the constellation, that a sex hormone alteration may underlie the increase in VAT, and that an increase in E/T may also directly contribute to the insulin defect (11). Of interest, a low testosterone level has been reported to be prospective for VAT accumulation in men (12).

If we are correct in attributing the constellation to an increase in VAT, then its components could also include any factor associated with VAT, such as plasminogen activator inhibitor-1, fibrinogen, factor VII, and C-reactive protein.

If interest in naming the constellation survives, and if our hypothesis is correct, I do not believe "metabolic syndrome" or "insulin resistance syndrome" would be appropriate names. Hypertension and hemostatic factors do not seem to be "metabolic," and "insulin resistance" would be a secondary factor. A better name might be

simply the "risk factor syndrome." Should an alteration in the sex hormone milieu be confirmed as underlying the increase in VAT, and the VAT in turn underlie the constellation, perhaps an appropriate name would be the "Glucose-Insulin-Lipid-Hypertension-Testosterone–Estrogen" or "GILHT-E" syndrome.

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